REMARKS/ARGUMENTS

The Present Invention

The present invention is directed to a method of treating cancer, a method of treating an immune-related disease, a method of preventing a cancer in a mammal, a pharmaceutical composition, a method for inducing apoptosis of a natural killer (NK) cell, a method of activating NK cell cytolytic activity, and a method of decreasing the number of NK cells in a host.

The Pending Claims

Claims 1-5, 8, 11-22, 25, 28-30, 58-63, and 68 are pending of which claims 1-5, 8, 11-22, 25, 28-30, 58, and 60-63 are withdrawn, and claims 59 and 68 are under examination.

The Final Office Action

The final Office Action indicates that the Information Disclosure Statement filed on August 8, 2007, has been considered. The final Office Action also contends that the effective filing date of claims 59, 66, and 67 is the filing date of PCT/US03/09707, namely March 23, 2003. The final Office Action maintains the objection to the specification for allegedly containing unlabeled trademarks. The final Office Action maintains the enablement rejection of claims 59, 66, and 67.

The final Office Action newly objects to the specification under 35 U.S.C. 132 (a) as allegedly introducing new matter. Specifically, SEQ ID NOs: 6-9 of the substitute Sequence Listing are allegedly new. The final Office Action further objects to the specification under 37 C.F.R. 1.75 (d) (1) as allegedly lacking antecedent basis for the language of claims 59, 66, and 67. Claim 67 is objected to for lacking the term "of" between "method" and "inducing."

Claim 67 is rejected under Section 112, second paragraph, as allegedly indefinite. Claims 66 and 67 are rejected under Section 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 59, 66, and 67 are rejected under Section 112, first paragraph, as allegedly containing new matter.

Reconsideration of the objections and rejections is hereby requested.

The Amendments to the Specification and Claims

The specification at paragraphs [0003] and [0021] has been amended to label the term "GenBank" as a registered trademark. Also, the specification has been amended to include the appropriate SEQ ID NO: (of SEQ ID NOs: 6-9) after the corresponding GenBank Accession No. in paragraph [0021].

Claims 66 and 67 have been canceled. Claim 68 has been added and is supported by the specification at, for example, the first sentence of paragraph [00132] on page 32.

No new matter has been added by way of the amendments.

Discussion of the Objections to the Specification and Claim

The final Office Action maintains the objection to the specification for allegedly containing unlabeled trademarks. Per the suggestion of the Office, the specification at paragraph [0021] has been amended to properly label "GenBank" as a currently registered trademark. The amendment to the specification, therefore, renders the objection moot.

The final Office Action objects to claim 67 for lacking the term "of" between "method" and "inducing." The rejection is moot, since claim 67 has been canceled herein.

The final Office Action newly objects to the specification under 35 U.S.C. 132 (a) as allegedly introducing new matter. Specifically, SEQ ID NOs: 6-9 of the substitute Sequence Listing are allegedly new. The final Office Action further objects to the specification under 37 C.F.R. 1.75 (d) (1) as allegedly lacking antecedent basis for the language of claims 59, 66, and 67.

SEQ ID NOs: 6-9 of the Sequence Listing submitted on August 8, 2007, represent the sequences of GenBank Accession Nos. AAG29348, AF254069, AAG29349, and AF254070, respectively. The sequences of each GenBank Accession No. were incorporated by reference into the specification of the instant application. The specification has been amended in paragraph [0021] to include the corresponding SEQ ID NO: after the recitation of the GenBank Accession No., such that there is antecedent basis, pursuant to 37 C.F.R. 1.75 (d) (1). Also, a Statement indicating that the amendatory material represents material incorporated by reference and that the application does not contain new matter is provided

herewith. Therefore, the requirements for a proper incorporation by reference have been met, and the objections under 35 U.S.C. 132 (a) and 37 C.F.R. 1.75 (d) (1) should be withdrawn.

In view of the foregoing, the objections to the specification and claim 67 should be withdrawn.

Discussion of the Enablement Rejection

The enablement rejection of claims 59, 66, and 67 has been maintained by the final Office Action. The rejection as it pertains to claims 66 and 67 is moot, since these claims have been canceled herein. The rejection as it pertains to claim 59 is traversed for the reasons set forth below.

The final Office Action alleges that claim 59 encompasses a method of inducing apoptosis of human NK cells using a polynucleotide encoding a human IL-21, whereas the specification allegedly demonstrates the induction of apoptosis in only mouse NK cells upon administration of only a mouse IL-21 polynucleotide. The final Office Action contends that there are fundamental differences between murine and human NK cells, such that it is highly unpredictable as to whether the method would function the same in human NK cells as in mouse NK cells.

The Office's position on the unpredictable nature of the claimed method cannot stand, because, the effect on NK cell number and NK cell cytolytic activity of a mouse IL-21 polynucleotide in a mouse was, in fact, predictive of the effect on NK cell number and NK cell cytolytic activity of a human IL-21 molecule in a human. As stated in the new Declaration Under 37 C.F.R. 1.132 of Dr. Warren J. Leonard, submitted herewith, patients received a recombinant human IL-21 molecule by intravenous bolus injection in an open-label, two-arm, phase I trial of human IL-21 for patients with malignant melanoma. The absolute number of natural killer (NK) cells decreased in the treated patients, whereas NK cell cytolytic activity in these patients increased. The effects observed in humans in this clinical trial parallel the decrease in the number of NK cells and the increase in NK cell cytolytic activity observed in mice, which were administered a mouse IL-21 polynucleotide, which observations in mice are described in the specification of the above-identified application at paragraph [00132] of Example 7. Accordingly, the rejection of claim 59 on the

basis that it is unpredictable as to whether one could extrapolate the mouse data into the human context is improper.

The final Office Action also contends that the disclosure of the instant application does not reasonably enable the full scope of the claims which encompasses contacting any NK cell from any species with a polynucleotide encoding SEQ ID NO: 6 or 8. One of ordinary skill in the art allegedly could not extrapolate the mouse data to any species without undue experimentation.

The enablement rejection on these grounds is traversed, because, as stated above, the effects of a human IL-21 molecule on human NK cells paralleled the decrease in the number of NK cells and the increase in NK cell cytolytic activity observed in mice, which were administered a mouse IL-21 polynucleotide. Therefore, the mouse data reasonably correlates with the claimed invention, including a method of inducing apoptosis in human NK cells with a human IL-21 polynucleotide. As such, the mouse data constitutes a working example of the claimed method invention.

The burden is now on the examiner to give reasons for a conclusion of lack of correlation for the animal model example. MPEP 2164.02 Applicants remind the Office that a rigorous or an invariable exact correlation is not required. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985).

The final Office Action further contends that claim 59 encompasses a method of administering *in vivo* an IL-21 gene to humans, thereby encompassing gene therapy. Because the art of gene therapy allegedly is problematic, unpredictable, and still in its infancy, the claimed method allegedly requires undue experimentation. The final Office Action relies on the teachings of Wang et al., *Cancer Res.* 63: 9016-9022 (2003) (hereinafter Wang et al.), which allegedly suggests that administering an IL-21 polynucleotide for the treatment of humans does not appear practical, citing to the second sentence of the second paragraph of the right column on page 9021. Accordingly, the final Office Action questions the enablement of the claimed invention.

The enablement rejection on the basis of the alleged teachings of Wang et al. is improper, because Wang et al. (at the second sentence of the second paragraph of the right column on page 9021) actually states:

> In this study, we have used a hydrodynamics-based gene delivery technique to generate sustained production of large amounts of circulating IL-21 protein *in vivo* to treat established s.c. tumors. Although this method may not be practical in the clinic, it allows us to effectively and efficiently study the *in vivo* biological effects of cytokines in small animals without producing large amounts of recombinant protein that is often a laborious, time-consuming, and expensive procedure limiting research.

Wang et al. at this instance actually teaches that the hydrodynamics-based gene delivery technique may not be practical in the clinic, but does not refer to any method of administering an Il-21 polynucleotide for the treatment of humans as alleged by the Office.

Furthermore, the teachings of Wang et al. does not affect the enablement of claim 59, since the state of the art at the time of filing the instant application was such that methods other than the hydrodynamics-based gene delivery were known in the art. See, for example, U.S. Patent 5,399,346, which was published on March 21, 1995.

Moreover, the art of gene therapy at the time of filing the instant application was not as unsuccessful at the time of filing the instant application, as the final Office Action alleges. As shown in the attached Declaration of Dr. Steven A. Rosenberg, which was previously submitted to the U.S. Patent and Trademark Office in connection with U.S. Application No. 10/701,022, gene therapy was successful in the case of at least two patients under his care: one who received a Tumor Necrosis Factor (TNF) gene and the other who received a T Cell Receptor (TCR) gene. As evidenced by the Declaration of Dr. Rosenberg, both of these patients have survived for more than 10 years due to the gene therapy. Data further demonstrating successful gene therapy in humans are disclosed in, for example, Blaese et al., *Science* 270: 475-480 (1995), Mullen et al., *Human Gene Therapy* 7: 1123-1129 (1996); and Onodera et al., *Blood* 91: 30-36 (1998); copies of which are attached hereto. Therefore, the final Office Action's position that the art of gene therapy is problematic, unpredictable, and still in its infancy is simply untrue.

The final Office Action further contends that the specification lacks any specific non-general guidance on how to induce apoptosis of NK cells in humans using the claimed methods. As stated above, the methods of delivering genes to humans were known in the art at the time of filing the instant application. Also, the amino acid and nucleotide sequences of both mouse and human IL-21 were known in the art. In view of the foregoing, the claimed invention in view of the specification and the state of the art is enabled. Applicants remind the Office that an inventor need not explain every detail since he is speaking to those skilled in the art. *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981). Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be. *In re Gay*, 309F.2d 769, 774, 50 CCPA 725, 733, 135 USPQ 311, 316 (CCPA 1962).

In view of the foregoing, the instant specification provides sufficient guidance, such that one of ordinary skill in the art was enabled to carry out the method of claim 59. Therefore, the rejection of claim 59 should be withdrawn.

Discussion of the Indefiniteness Rejection

Claim 67 is newly rejected as allegedly indefinite for the recitation of "biological activity." Claim 67 has been canceled herein. Therefore, the rejection is moot. Applicants therefore request that the indefiniteness rejection is withdrawn.

Discussion of the Written Description Rejection

Claims 66 and 67 are newly rejected as allegedly lacking written description. Specifically, the final Office Action contends that the full breadth of the claims is not supported. Claims 66 and 67 have been canceled herein. Therefore, the rejection is moot. Applicants therefore request that the written description rejection is withdrawn.

Discussion of the New Matter Rejection

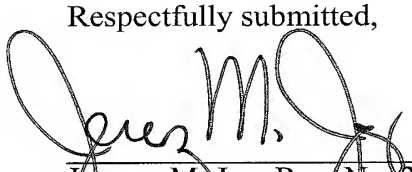
Claims 59, 66, and 67 are newly rejected as allegedly containing new matter, since each claim was previously amended to reference SEQ ID NOs: 6 and 8, which sequences were incorporated by reference to GenBank Accession Nos. AAG29348 and AAG29349, and the specification allegedly does not include the material incorporated by reference. The

rejection is traversed, because the specification was amended to include the material that was incorporated by reference by way of adding SEQ ID NOs: 6 and 8 to the Sequence Listing submitted on August 8, 2007. Also, the specification has been amended herein to recite the SEQ ID NOs: after the GenBank Accession No. in paragraph [0021] to which the sequence corresponds. Further, a Statement Under 37 C.F.R. 1.57 (f) stating that the amendatory material represents material previously incorporated by reference and that the instant application does not contain new matter is submitted herewith. Applicants therefore request that the new matter rejection be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



Jeremy M. Jay, Reg. No. 33,587
LEYDIG, VOIT & MAYER
Two Prudential Plaza, Suite 4900
180 North Stetson Avenue
Chicago, Illinois 60601-6731
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

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